

ESSAY FOR WELLCOME PRIZE.

THE HISTORY OF OUR KNOWLEDGE

REGARDING THE

FUNCTIONS

OF THE

PITUITARY GLAND.

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## INTRODUCTION.

The Pituitary is one of the series of glands termed the Endocrine Organs and as such, it plays a very important function in the vital activities of the body. Despite its importance however, it is only comparatively recently that investigations have been made regarding its functions in the human machine.

The presence of such a thing as internal secretion was unknown until 1849, when BERTHOLD 1, conducted his experiments on the transplantation of the cock's testis. In the same year there appeared ADDISON'S 2, monograph attributing a definite clinical syndrome to a destructive process of disease of the suprarenal capsules. The idea was given a further impulse by BERNARD'S (1855) classical experiments on hepatic function showing the existence of an internal secretion (glycogen) in addition to an external secretion (bile). 3. The relation of glands of internal secretion to disease being proven, BROWN-SEQUARD'S inestimable service (1869) in introducing the idea of organotherapy came in due course.

From the earliest times the pituitary body has been regarded as an organ possessing a secretory function. GALLEN and VESALIUS believed that the mucus (pituita) formed in the brain was excreted by the agency of the pituitary body. Later authors however, (WILLIS, VIEUSSSENS, SYLVIUS, BOERHAVE, and MONROE,) inclined to the view that the cerebro-spinal fluid was secreted.

secreted by that organ. RICHARD LOWER in <sup>a</sup> remarkable tract *Dissertatio de Origine Catarrhi*. (1672) was the first to experimentally disprove the Galenic doctrine. "For whatever Serum is separated into the ventricle of the brain and tissues out of them through the Infundibulum to the Glandula Pituitaria distills not upon the Palate but is poured again into the blood and mixed with it." Previous to this (1660) SCHNEIDER had cast doubt on the Galenic theory in his treatise *De Catarrhis*. THEOPHILE de BORDEU 4. the first to state clearly the function of the internal secretions - in his anatomical researches, writes that the ancients thought that the office of the pituitary body was to empty its humors through the nostrils - the moderns holding that it sent them to the sinuses of the sella turcica, while he also indulges in a few vague conjectures as to the possibility of the passage of the pituitary secretions into the circulation.

MAGENDIE 5. (1842) who investigated the genesis of the cerebro-spinal fluid regarded the hypophysis as an organ resembling the lymph glands and he believed that it collected the lymph from the brain and conveyed it into the circulation.

LIEGELOIS 6. (1860) was the first to include the hypophysis among what were known as the blood glands. He described histological findings which he believed pointed to the formation of blood in this organ. (It is interesting to note that the brothers WENZEL 7. believed that epilepsy was due to an accumulation of colloid in the hypophysis.)

After the conception of the doctrine of internal secretion by Brown-Sequard, a large number of observations were published which sufficiently justify the inclusion of the pituitary body among the internal secreting organs. The fundamental argument was found by ROGOWITSCH 8. (1889) who discovered that extirpation of the thyroid was followed by hypertrophy of the hypophysis. The decisive evidence however was brought forward by MARIE 9. (1886) who, under the name of Acromegaly, described a clinical condition, not sharply separated from gigantism, which had previously

attracted the attention of a certain number of authors (FREIDREICH 10. -hypertosis of the skeleton, FRITSCH & KLEBS 11. -gigantism.) In combination with MARINESCO (1891) MARIE showed that changes of the hypophysis - generally tumours, are invariable in this condition and it seemed from this that the cause of the peculiarities of growth must lie with the pathological condition of the hypophysis. 12.

This momentous discovery of Marie excited an immense amount of interest in the clinical and pathologico-anatomical aspects of anomalous development, while at the same time it pointed to the hypophysis as the centre of interest. These researches extended to the morphology of the organ and its pathological changes, with the result that a considerable number of facts have been brought to light which largely explain its functional activity.

Physiological research was first conducted by means of experimental extirpation. An important advance was made by OLIVER & SCHAFER 13. (1894) who discovered that the watery extract of the hypophysis possesses distinct physiological properties, but let us, in our study, first discuss the history of the discovery of the structure of the gland.

#### HISTORY REGARDING STRUCTURE.

The Pituitary Body or Hypophysis Cerebri, as it is often called, lies in a bony hollow in the base of the skull - the Sella Turcica, and it is attached to the floor of the third ventricle by a stalk called the infundibulum.

It consists of two lobes; - the anterior, which is named the Pars Anterior, and the posterior, which is further subdivided into Pars Intermedia and Pars Nervosa. Some of pars intermedia extends upwards on to the stalk and is wrapt round it to form the pars Tuberalis. Between the two lobes is a small space the Pituitary Cleft.

The pituitary body arises as two quite independent growths; the partes anterior, intermedia and tuberalis coming from buccal ectoderm, while pars



nervosa comes from neural ectoderm. The buccal ectoderm consists of a hollow upgrowth from the buccal mucous membrane - the persistence of the hollow giving the pituitary cleft. This buccal upgrowth is originally epithelial tubules, but they lose their lumina and hence pars intermedia and pars anterior consist of circular masses of epithelial cells. This was shown first by RATHKE 14. (1838), developed by BALFOUR (1874) and GOTTE (1875) and finally elucidated by MIHALKOWICS 15. (1875) while more recently HERRING 16. (1908) has summed the matter up in a paper on the subject.

The buccal upgrowth is joined by a hollow downgrowth from the floor of the third ventricle consisting of neuroglial tissue. This latter loses its hollow in the infundibulum but retains its connection with the brain, and so, at birth, the pituitary body is represented by a single structure, unconnected with the mouth but connected to the floor of the third ventricle.

PEREMESCHKO 17. (1867) appears to be the first to have described the three parts of the gland - anterior, intermedia and nervosa. The pars tuberalis was distinguished much later by HERRING, while TILNEY discussed its histological aspect.

The microscopic structure of the gland although at first appearing insignificant in considering the functions of the pituitary body, is nevertheless of the greatest importance as it was by the study of the structure of the individual parts that various workers were able to evolve theories of pituitary function which experimental evidence has confirmed.

Let us consider each part in turn and deal with the history of the discoveries in connection with them.

PARS ANTERIOR is composed of nests of epithelial cells - from the original tubules. These cells are of two types, granular and non-granular, as shown first by DOSTOIEWSKY 18. (1886) and LOTHINGER 19. (1886). The granular cells are stainable and hence are called "chromophil" and are further subdivided

into (a) those, the granules of which stain with acid dyes (eosinophils) and (b) those, whose granules stain with alkaline dyes (basiphils). The nongranular or clear cells are non-stainable and hence are termed "chromaphobe." It has been suggested that the chromaphobes are discharged forms of the chromaphils but this is open to discussion and BAILLEY 20. (1921) and COOPER 20. (1925) have shown that these cells appear to develop along diverging lines. Various workers have made observations regarding the minute structure of the cells of the anterior lobe, <sup>and</sup> although these in themselves are of little importance, they have all helped in the composition of a definite theory of anterior pituitary secretion. These may be briefly summarised; -

LAUNOIS 21. (1904) investigated the chromaphil cells and further classified them. It is believed that the Golgi apparatus is always on the side of the nucleus which corresponds with the pole of discharge of a secretory cell. REISS 22. (1922) found that the Golgi apparatus differed in position in the different chromaphil cells and suggested that there are two kinds of secretion - one being stored in the vesicles, the other being passed into the blood. It is generally agreed that the secretion passes into the blood, and colloid material has been shown to be present in the pars anterior capillaries by LAUNOIS and the GRUNBAUMS 23. (1911). The chemical structure of the colloid has been investigated by various workers (PIRRONE 24. (1904), GUERRINI 25. (1904), LAUNOIS 21. (1904), THAON 26. (1907), SIMPSON & HUNTER 27. (1910) and HALE-WHITE 28. (1913)) while the changes in the pars anterior during pregnancy and other anomalous conditions have been investigated by many workers; - COMTE 29. (1898), LAUNOIS & MULON 30. (1904), JORIS 31. (1908), STUMME 32. (1909), KOHN 33. (1910), FRY 34. (1915) ADDISON 35. (1917) and KOJIMA 36. (1917).

It is largely by the utilisation <sup>of</sup> the small but important details brought forward by these observers that the functions can be attributed to the specific parts of the anterior lobe of the pituitary, and although

some of the observations of the workers are invaluable, a great deal of them have yet to be appreciated and coordinated with other facts in order to further the knowledge of the functions of the anterior lobe. The observations of experimenters who either removed or supplied excess of the anterior pituitary to experimental animals are exceedingly useful in this respect and the history of these experiments will be considered later.

PARS TUBERALIS was first described in detail by TILNEY 37, (1911) and corresponds to what was termed by HERRING 38, (1908) as "the tongue-like process," but so far no very definite results have been obtained by investigations into its functions. The main work in this direction was performed by ATWELL & MARINUS 39, (1913) and by MARINUS 40, (1919) and will be considered later.

PARS INTERMEDIA has been investigated by various workers. The most important observation in this respect was that made by HERRING 38, (1908) and confirmed by BEVACQUE 41, (1911) of the presence of vesicles in this part of the gland, which tended to accumulate at that part of the intermedia adjacent to the pars nervosa. In addition there was shown to be present certain other masses of a similar substance not enclosed in vesicles. These have been termed "Herring's Bodies" and are traceable into and through pars nervosa, and can even be seen passing into the infundibulum of the third ventricle. Apparently they undergo a chemical transformation, as extracts taken from different parts of their course have according to Herring pronounced differences in their physiological results. Corroborative evidence with respect to the secretory activity of the cells of the pars intermedia of the pig has been furnished by LEWIS & MAURER 42, (1920).

Herring's observation serves as a prominent landmark in the discovery of the method of secretion of the pituitary gland. These results have been checked by HALLIBURTON, CANDLER & SIKES 43, (1909) while in addition they were corroborated by experimental evidence when CUSHING & MADDOCK 44, blocked the

infundibular stalk passage with a small silver clip, and found that the pars nervosa became greatly distended as a result of the accumulation of "Herring Bodies." CUSHING & GOETSCH 45, in 1910 showed that the same active principles were present in the Cerebro-Spinal Fluid as in the posterior lobe of the pituitary, and hence further corroborated the work of Herring. Other workers to verify these findings were COW 46, (1915) and DIXON 47, (1928).

Herring's work directed the attention of experimenters to the cerebro-spinal fluid, and a large number of observations were conducted in this connection. Some of these were of extreme importance and indeed, it was mainly by them that the various functions of the posterior pituitary were discovered.

DIXON & MARSHALL 48, (1924) found that extracts of ovary of a pregnant animal injected into another animal activated the pituitary and caused the C.S.F. to produce uterine contraction. TRENDLENBURG 49, observed that the C.S.F. contains an active principle which produces contraction of the uterus. G. & M. OEHME 50, found that the C.S.F. contains a principle causing vaso-constriction. These results have been corroborated by MAYER 51, and by MIURA 52, (1925).

PARS NERVOSA has been investigated by a large number of workers and is exceedingly important due to the presence in it of "Herring Bodies." Herring showed that these are greatly increased in amount after thyroidectomy and MOTT 53, has found that it is the same with Myxoedema, (1917). Similar masses were seen by CROWE, CUSHING & HOMANS 54, (1909) in the neighbourhood of grafts of the pituitary into cerebral tissue. While JORIS 51, (1908) has shown that there is an increase in size of the pituitary with pregnancy, and also that more cells pass from pars intermedia into pars nervosa when the person is in this condition.

In connection with the blood supply, it is difficult to attribute to any particular workers the credit of finding the different conditions of supply. However GENTES 55, published an account of the blood vessels in 1908 and later (1910) DANDY & GOETSCH did



likewise. 56. The pars anterior and pars tuberalis are very vascular. Pars nervosa is slightly so, but no blood vessels are to be found at all in pars intermedia unless it is very thick, when a few may be perceived. This difference in blood supply is very important, as by considering the varying amounts of blood passing through the different parts of the gland, we can surmise the routes of secretion; and, in this way, it was concluded that partes anterior and tuberalis secreted direct into the blood, while partes nervosa and intermedia probably had no such secretion. With the exception of the secretions of pars tuberalis, the route of which is not yet known, such suppositions have been shown to be correct.

#### HISTORY OF EXPERIMENTS IN CONNECTION WITH THE REMOVAL OF WHOLE OR PART OF THE PITUITARY.

It was HORSELEY 57. (1885) who, in order to compare the results of the removal of the hypophysis with those which follow thyroidectomy, first undertook the extirpation of that organ. His experiments like those of DASTRE (1889) and of GLEY (1891) were completely negative, the animals dying after the operation.

Following the theory propounded by MARIE & MARINESCO 12. (1891) concerning the Pathogenesis of acromegaly, MARINESCO 58. (1892) next carried out extirpation experiments with cats. Since that date hypophysectomy has been performed on animals of different species, and according to various methods. The animals most frequently employed were the cat and the dog, although a certain amount of material has been supplied by other animals (Frog-tortoise-hen-and-rabbit).

Experimental extirpation from the oral cavity, of the hypophysis of frogs, as carried out by CASELLI 59. (1900) did not yield results of any value. GAGLIO 60. (1902) operated on frogs and tortoises by the same method, however, and found that, though some of his animals died very shortly after, apparently as a result of ineffective conditions, others lived from 1½ to 33 months without pathological symptoms.



BOTEANO 61. (1906), a pupil of Paulesco, describes the extirpation of the hypophysis of frogs by the supra- and latero-cranial methods; he found that two to three days after total extirpation, his animals invariably died with symptoms of neuro-muscular asthenia, while control animals operated on by the same method, the hypophysis being only partially removed or left intact, remained perfectly normal, with the exception of slight symptoms of central nervous stimulation.

FICHERA 62. (1905) operated on hens and the results of his experiments led him to conclude that, in young hens, the hypophysis is not essential to life, and that the symptoms that follow its removal are in no way char<sup>acter</sup>istic or constant. The extirpation experiments of GLEY were of no account owing to faulty technique, and the same may be said of those of MONACO & VAN RYNBERK who worked with rabbits. Experiments with cats and dogs have been more successful however, and a large number of workers have employed these animals; - MARINESCO 58. (1895); VASSALI & SACCHI 63. (1892); CYON 64. (1901); CASELLI 59. (1900); GATTA 65. (1896); BIEDL 66. (1912); FREIDMAN & MASS 67. (1900); DALLA VEDOVA 68. (1903); PIRONE 24. (1904) and GEMELLI 69. (1908). The method which was first adopted and later was in most frequent use was that of opening up the hypophysis from the base of the cranium by way of the oral cavity. The organ was usually destroyed by thermo-cautery or by the injection of chromic acid. removal was effected with spoon forceps, generally of the operators own design.

N. C. PAULESCO 70. (1906) introduced a new method of hypophysectomy when he employed the lateral approach beneath the temporal lobe. A large aperture was made in each side of the skull, and the hemispheres were pushed across to one side in order to obtain good access to the gland. This technique was specially applicable to dogs, but is unsuitable as regards cats owing to the depth of their sella, and <sup>a</sup> further method was evolved by N. M. DOTT 71. (1922) for such animals, in which a trocar was introduced along the lateral

margin of the orbit through the sphenoidal fissure into the sella turcica. This method causes little or no damage other than the destruction of the hypophysis.

Surgical interference in the human subject is an entirely different problem, and the various methods employed are described by BLAIR BELL, 72, (1919).

PAULESCO 70, (1907) was the first to state definitely that complete removal of the pituitary body is always fatal. These results were obtained from all types of vertebrata, and were confirmed by CUSHING 73, (1909) <sup>and fellow workers</sup> who experimented mainly on dogs. They 74, found moreover that death occurred more rapidly with old than with young dogs, and ascribed this to the presence of accessory glands in young animals. They however differed from PAULESCO in one respect; namely that he said that section of the infundibulum was fatal, while they found that such was not the case. Cushing found that removal of part only of the <sup>Cushing found that of part only of the anterior lobe</sup> anterior lobe lead to certain definite changes in metabolism, which he thought were due to deficient secretion - this latter condition he termed "Hypopituitarism."

These results have been substantiated by the work of BIEDL 66, (1912); B.A. HOUSSAY 75, (1916); ASCOLI & LEGNANI 76, (1911-1912); BLAIR BELL 72, (1910) and of DOTT 71, (1923); --

BIEDL and HOUSSAY performed a series of experiments in this connection, and both found that complete removal of the pituitary body was fatal.

BLAIR BELL completely removed the pituitary in five dogs and death ensued in each case <sup>within</sup> within thirty-six hours.

DOTT effected nine complete removals and death occurred in less than two weeks in each case. Dott also found that death followed sooner in old dogs than in young animals.

Most of these observers came to the conclusion that removal of the whole of the anterior lobe has the same effect as complete extirpation of the gland, while removal of the posterior lobe causes no definite symptoms.

In some of Cushing's later experiments death did not always occur, or at any rate was delayed, but as he pointed out this could be caused by the leaving of some of the gland behind. Cushing found that life was prolonged but not to any great extent, by transplanting the gland to some vascular system.

ASCHNER 77. (1912) did not find the gland essential to life or at any rate, obtained a considerable prolongation of life after its removal, but freely admits that he did not entirely extirpate the gland, and that fragments were frequently left behind. In all his cases symptoms of hypopituitarism showed themselves rather than those of apituitarism. There was little sexual development, while physical development was retarded to a lesser degree. In the adult, removal of the pituitary resulted in the laying down of fat, while the body temperature fell  $1^{\circ} - 1.5^{\circ}$  below normal. These effects were also obtained by removal of the anterior lobe alone. The output of  $CO_2$  was found to be diminished after removal of either the whole pituitary body, or of only its anterior lobe. This was shown in dogs by BENEDICT & HOMANS 78. (1912) and in frogs by WINTON & HOGGEN 79. (1923), who also demonstrated that a permanent pallor of the skin occurs in hypophysectomised frogs due to the contraction of melanophores.

All these experiments quoted above tend to show that the pituitary body is essential for life, and that its removal is fatal either immediately or a short time after the operation. However another school of thought has evolved from the work of several different observers, who claim to have extirpated the gland and yet to have found that death did not ensue as a result. These experiments may be summarised;—

HORSLEY & HANDELMANN 80. (1912) who extirpated by operation through the base of the skull, state that they found that although a large proportion of their cases died within forty-eight hours, they consider this was due to causes due to the operation, (shock, haemorrhage or infection). Those that survived showed no symptoms of apituitarism or of hypopituitarism.

\* CAMUS & ROUSSY 81. (1922) came to the conclusion after 150 cases of hypophysectomy that the gland is not essential to life, and that the symptoms described by other workers are due to injury to the tuber cinereum. It is of interest to note that most of their experiments had fatal terminations within a few days of the operation.

C.G. BROWN. 82. (1922) comes to a similar conclusion as the last observers, and attributes the death of a greater part of his experimental subjects to faulty technique or lack of asepsis.

SACHS & MACDONALD 83. (1925) said that removal was never fatal unless the base of the brain was injured. They also attribute accompanying polyuria to a lesion of this area.

DANDY & REICHERT 84. (1925) removed the pituitary from 31 dogs and cauterised the base of the brain in that region, and found that the animals survived a fair amount of time (18 - 138 days.).

From a point of view of knowledge, partial removal and lesions of part of the pituitary have been more important than complete extirpation. Most of the work in this respect has been already quoted. The experiments of ASCHNER 77. (1912) are perhaps the most important in this direction, as several definite conclusions were drawn on viewing the results. He showed that the pituitary is concerned with growth. By removing part of the pituitary of one of a litter of dogs and comparing its growth with that of the other dogs, he found that there was retardation in growth, which showed itself, not only by general diminution in size, but also in a delay in the ossification and in the growth of bones. He also showed that sexual development was retarded, and indeed, in some cases underwent retrogression. The mental faculties were dimmed, and the basal metabolism and all connected with it (i.e. temperature, activity, etc.) were reduced, and possibly as a result of this, he found that marked obesity occurred. This was so apparent that despite its discrepancy in stature, the experimental animal often weighed more than the control animals of the litter.



This latter observation was confirmed by the work of LIVON 85. (1911) who damaged the pars anterior of a dog, and found that there was pronounced laying down of fat. (3-4 cm.). These conditions were termed "*Dystrophia Adiposa Genitalis*." or "*Frohlich's Syndrome*." after an Austrian neurologist named FROHLICH 86. (1901) who first investigated the disease.

PAULESCO 70. found that section of the infundibulum was fatal, but no other experimenters confirmed this, and indeed, BLAIR BELL 87. (1917) showed that section of the stalk produced symptoms of *dystrophia adiposa genitalis*. CUSHING & MADDOCK 44. obtained similar results to Blair Bell by blocking the passage along the infundibular stalk by means of a small clip.

P. E. SMITH & J. B. GRAESER 88. obtained Frohlich's Syndrome by injecting chromic acid into the pituitaries of rats, while DOTT procured the syndrome either by partial removal of the anterior lobe or by cutting the stalk; and he also found that injection of anterior lobe extracts tended to bring the conditions back to normal, but not completely so.

In connection with the effect of the pituitary body on bone formation, it is extremely interesting to note that NUVOLI 89. (1923) produced rickets in rabbits by exposing the pituitary body to the influence of X-rays for ten minutes a day. But this historical fact, although generally credited, has to be considered with reserve owing to the extreme difficulty of confining the rays to the pituitary body, <sup>allowing them</sup> and not <sub>upon</sub> any of the surrounding structures also.

Several workers have brought to notice the fact that Polyuria often follows a Pituitary lesion. CUSHING 90. (1913) obtained polyuria after excision of the posterior lobe, while HOUSSAY & RUBIO 91. (1923) obtained it after hypophysectomy, and several others have demonstrated the fact that mere manipulation or injury to either the posterior lobe or to the whole pituitary is followed by polyuria usually. 92.

CAMUS & ROUSSY 93. hold that the polyuria



is due to injury to the part of the brain adjacent to the pituitary, and not to the pituitary itself, and indeed, even go as far as to say that injuries to the tuber cinereum are responsible for most of the conditions at present attributed to the pituitary. They are supported by experimental evidence furnished by CAMUS & GOURNAY 94, (1924) and also by BAILEY & BREMER 95, and other workers, 96. HOUSSAY 97, confirms the polyuria from lesions of the tuber cinereum, but considers that the action may nevertheless be produced through the gland, and in cooperation with HUG 98, he supported his view experimentally.

OEHME 99, (1919) completely denervated the kidney, and found that injury to the tuber cinereum produced polyuria, and hence, in this way, showed that the stimulation was "humoral" rather than "nervous." This experiment has been performed by several other workers, 100, who obtained confirmatory results. They all found that in addition there was an interval of about a day before the polyuria became manifest.

Independent papers of FRANK 101, (1924) and E. SHARPEY-SCHAFFER, 102, (1925) criticise the view of Camus and his supporters, and point out that they have ignored the existence of pars tuberalis. In addition Frank and Sharpey-Schafer utilise the observations of Oehme and his corroborators to support their own view - saying that the polyuria is the result of an indirect action through the pituitary rather than an immediate effect of the brain lesion.

#### THE IDEAS REGARDING THE FUNCTIONS OF THE

#### GLAND AS DERIVED FROM CLINICAL EVIDENCE.

Many of the ideas regarding the functions of the pituitary body were derived by consideration of the results of diseased conditions of the gland. Hence, owing to the large number of observers, who brought to notice peculiarities due to the non-function or to the mal-function of the gland, it is practically

impossible to give a complete list. Such a course would not help to any extent, but would only tend to confuse the issue. The main observations only in this direction will be given, with as far as possible only the principle names.

The first disease which was definitely associated with the pituitary body was Acromegaly, "a peculiar, non-congenital hypertrophy of the upper, lower, and cephalic extremities." P. MARIE 9, (1886) gave the name to this peculiar condition, but it was MIN KOWSKI 103, (1887) who first connected the condition with mal-function of the pituitary body. The announcement by Marie in 1886 of the discovery of this disease - acromegaly, led to a great amount of interest being taken in the subject. Old medical literature was ransacked and as a result, it was found that the earliest medical description of the syndrome appeared to be that of SAUCEROTTE in 1772, 104, while many other reports of acromegalics were unearthed. LANGER 105, (1872) described in detail the skeletal changes, and he attributed the enlargement of the sella turcica to disease of the hypophysis. Several other observers have described post-mortem findings on acromegalics. However, probably owing to their wide distribution, and to their report in rather obscure publications, these observations were not correlated prior to 1886. STERNBERG 106, published a collective review in 1899, and this appears to be the first general paper on the subject.

However, MARIE, associated later with MARINESCO 12, (1891) was the first to give a complete account of the syndrome, although at first he appears to have considered that the enlargement of the gland was the result rather than the cause of the condition. Later he thought that acromegaly was due to a disease, destructive of the gland, since in several post-mortems he found therein what he thought to be a tumour of a malignant character. It was due to this idea, that extirpation and destructive experiments were first performed in order to produce an increase in growth. The opposite result occurred however; instead of

acceleration of the growth, retardation took place. In this way it was recognised that the tumours of the pituitary body giving rise to acromegaly, were adenomal. BENDA 107. (1900) was the first to realise this, and he found that the enlargement was due to increase in the number of the eosinophil cells.

Various workers have identified themselves with the description for the first time of the different characteristic features associated with this syndrome, but that is outwith the scope of this essay. It is of interest to note however, that attention was first drawn to X-ray studies of the pituitary fossa by OPPENHEIM 108. in 1899.

Another work which is also extremely interesting is that of L.P. MARK 109. (1912) who himself suffered from the disease, and published an account of his personal experience and of the subjective symptoms.

The more important observers who have published papers on Acromegaly are CUSHING 90. (1912); BLAIR BELL 72. (1919); FALTA 110. (1915); BIEDL 66. (1910) and BASSOE 111. (1922).

The correspondence between acromegaly and gigantism, although not their relationship to the pituitary, appears to have been first pointed out by CUNNINGHAM (1872) and later by MASSALONGA 112. (1892). This latter worker also reports several cases of acromegaly in which the sella turcica is the normal size.

The fact that acromegaly and gigantism, in which there is an exaggerated growth, were accompanied by an enlargement of the pituitary, gave rise to a supposition that in dwarfs the reverse should be the case, (i.e. the pituitary should be smaller in proportion than usual) If such was so, it could be definitely shown that the pituitary was concerned with growth - hence several workers carried out observations regarding this point. Some however, found that in dwarfs, the pituitary was smaller than usual, others that it was of normal size, while others again found that it was larger than usual. It was pointed

out however, that in those latter cases, the enlargement was not due to a swelling of the gland, but either to cysts which had destroyed the anterior lobe or to tumours outside the gland pressing on it. Comparatively few examples have been brought forward, and probably the best known is one described by SIMMONDS 113. (1919), in which the anterior lobe was completely destroyed by cysts, the posterior being normal. In this way, as Simmonds pointed out, the growth-promoting function of the anterior lobe could be negatively inferred.

A further anomalous condition which has been attributed to unusual function of the pituitary, is Dystrophia Adiposa Genitalis or Frohlich's Syndrome, in which there is adiposity and genital atrophy.

This disease was first conclusively described by FROHLICH 86. in 1901, and as he then said it was due to deficient secretion (or hypopituitarism) while BARTELS 114. (1908) gave it the other name of dystrophia adiposa genitalis.

Dr. GARRISON 115. (1915) of the library of the Surgeon General of the U. S. Army, after reviewing the history of the condition states that the earliest report of the disease was that of B. MOHR. 116. (1840). Many other cases of similar description were reported prior to that of Frohlich, but no one definitely associated the syndrome with mal-function of the pituitary until he did.

At the meeting of the Ophthalmological Society of the United Kingdom in 1887, as reported in the British Medical Journal 117. however there occurred a remarkable discussion of the subject of pituitary lesions, and also their relation to the eye symptoms, obesity, menstrual disturbances and mental manifestations.

Quoting from the B. M. J. of that year;--

"Mr. J. B. Story (Dublin) read an account of the case of a young woman who gradually became blind in the right eye, and had temporal hemianopia in the other eye. She suffered from headache and slightly from vomiting. One of the things she complained of most was drowsiness about midday each



day. It was noticed that she got much stouter. She also suffered from irregular menstruation. At the time of reporting the case she was in fair general health, and able to follow her occupation (that of a dressmaker).---Mr. Nettleship remarked that a very similar case had been recorded in the Society's Transactions, and in that case, after death, a tumour was found in the pituitary fossa. Other similar cases had been published, and he had lately seen a case at St. Thomas's Hospital where the same train of symptoms had been produced in the same way.---Dr. Hill Griffith said that he had placed on record a case identical with that of Mr. Story. Cessation of menstruation and sleepiness had been present in his case; and, in several cases that he had seen, the patients had complained of getting stout.---Dr. James Anderson briefly<sup>described</sup> the case he had published, which closely agreed with that of Mr. Story. He said that it was the rule in pituitary tumours that the patient should get very stout.---Dr. Coupland mentioned also the concurrence of an increased development of fat in conjunction with disease or enlargement of the pituitary body."

It can be seen from the above quotation that, although at that time no one definitely understood the question, they were beginning to connect the idea of growth with the pituitary body.

Several cases of Dystrophia Adiposa Genitalis have occurred accidentally through the destruction of part of the pituitary, as for example by the passage of a bullet through the posterior lobe. This rather conclusively demonstrates the fact that the pituitary has something to do with growth. The classical example of such a case was one quoted by MADELUNG, 118. (1903). As a result of these observations, experimental injuries to the pituitary body were made by several workers. (BLAIR BELL, 87. LIVON, 85. BAILEY 92. and DOTT 71.) and it was found that in each case appearances similar to those with Frohlich's Syndrome arose.

BLAIR BELL found that section of the



stalk had similar results to partial removal of the anterior lobe; in both cases there was symptoms of dystrophia adiposa genitalis. LIVON obtained corresponding results by partial removal of the anterior lobe; BAILEY blocked the stalk by pressing gutta-percha on to it after trephining, while DOTT held that the constant factor in all cases showing this syndrome is injury to the pars anterior or interference with its blood supply.

According to ENGELBACH 119. (1925), when the pituitary insufficiency is restricted to the pars anterior, there results sexual infantilism without adiposity, but if the deficiency extends to pars posterior, then adiposity occurs as well. SHARPEY-SCHAFER 120. (1926) finds that the syndrome is associated with deficiency of posterior lobe secretion, and if this is accompanied with deficiency of the anterior lobe the stature remains small, but if the anterior lobe secretion is normal or increased the person becomes much larger than normal.

## HISTORY OF DISCOVERY OF THE EFFECTS OF POSTERIOR LOBE EXTRACTS.

### A. On the Circulatory System.

In the year 1892 G. OLIVER of Hull came to Sir Edward Sharpey-Schafer, or as he was at that time E. A. SCHAFER, and said that he had invented an instrument which he termed an "Arteriometer," and with which he claimed that he could measure the diameter of the radial artery at the wrist. He said that he had been surprised to find that various drugs (mainly extracts from different organs of the body) had varying effects on the diameter of the artery.

This interested Schafer extremely, and in cooperation with Oliver he conducted a series of experiments. 18. At first they used the arteriometer only, but soon however they extended their field and made use of other instruments in order to find out the different effects caused by the extracts, and eventually discarded the arteriometer as they realised that it

was not accurate enough for the work. Among the extracts tried was one of the pituitary body, and they found that when it was injected into a vein a rise in blood pressure occurred with contraction of the arteries and increase in force of the heart beats.

HOWELL 121. (1896) found that this effect was confined to extracts of the posterior lobe and this was later (1899) confirmed by SCHAFER & VINCENT 122. who also obtained a depressor effect. Other observers who have confirmed the depressor effect are HAMBURGER 123. (1904); LEWIS, MILLER & MATHEWS. 124. (1911) and JACOBSON 125. (1920), but in 1915 another paper was produced which showed that a depressor effect following the injection of <sup>the extract of</sup> an organ signifies nothing. 126. as it is caused by organic materials of a specific nature varying in different organs.

On considering the experiments in this direction in detail, a great diversity in both observations and opinions is manifest, and at present there still exists much doubt as to the exact action of the posterior pituitary on the circulatory system.

SCHAFER & OLIVER found that the force of the heart beat was increased, but other workers (C. TIGERSTEDT & V. AIRLIE. 127. 1913.) found that it was first decreased.

BECO & PLUMIER 128. (1913) showed that, with the heart in situ, the injection of posterior pituitary causes slowing of the heart (usually but not always) and that the effect is abolished by the injection of atropine, and partially so, by section of the vagus. Large doses of posterior pituitary have been shown by CLAUDE & PORAK 129. (1913) to affect the conductivity of the A.-V. Bundle, while the posterior pituitary does not paralyse the sympathetic nerves according to MATTIROLO & GAMMA 130. (1914).

If posterior pituitary is added to isolated heart, it has been found that the force and rate of the contractions are diminished. This was first shown by HERRING 131. (1904) in the frog and later by BECO & PLUMIER 128. (1913) and RESNIK & GEILING 132. (1925) in the mammal. All these workers

found that the effect was abolished by the injection of atropine, and hence, as a result of this series of experiments it has been surmised that the posterior pituitary secretion tends to stimulate the ends of the vagi; when these are paralysed with atropine then the stimulation of the sympathetic becomes manifest.

The history of the work in connection with the action of the posterior pituitary on arteries is very involved owing to the large number of workers who have engaged in the observations. Most observers found that there was vaso-constriction and a rise in blood pressure, and indeed, such was the case with OLIVER & SCHAFER 13. (1895) in their first experiments in this connection, but others (FROHLICH & PICK 133.) (1913) state that dilatation takes place with a fall in blood pressure.

Varying results have been obtained with different animals under different anaesthetics, and it has been found difficult to select the experimenters whose work has definitely helped in the advancement of the knowledge of the functions of the pituitary. Much work has been done to give negative evidence, and in this respect is just as valuable as that which gave positive results.

OLIVER & SCHAFER 13. (1895) found that a posterior lobe extract injected intravenously, caused a rise in blood pressure in the systemic circulation. This is accompanied in some animals by a fall in pulmonary pressure, as shown first by WIGGERS 134. (1911) and later by HALLION 135. (1914). A further injection often causes a fall in systemic pressure and a rise in the pulmonary. Hence SCHAFER & VINCENT came to the conclusion that there were two antagonistic posterior lobe principles, one causing constriction of the vessels, the other causing dilatation, and this latter they found to be soluble in alcohol.

The extract of the posterior lobe if injected subcutaneously has been shown by a large number of workers to cause a gradual rise in blood pressure with a slowing of the heart beat, which at the

same time is strengthened. This was first demonstrated by PARISOT 136. in 1908, but PORAK 137. (1922) on the other hand, found that there is a fall in blood pressure and not a rise. ABEL & GEILING 138. (1924) obtained both the oxytocic and the pressor effects from extracts of the nervous tissue of the infundibulum close to the stalk, and found that extracts of the brain substance itself have the effect of lowering the blood pressure. It is of interest to note that in 1912 HOUSSAY & GIUSTI 139. described a slight pressor effect from extracts of the floor of the third ventricle.

The posterior pituitary causes different effects in the different parts of the circulatory system. Various workers have identified themselves with these observations, most of them investigating some particular part of the system. It was found that the posterior lobe extract tends to produce contraction of most arteries, including the aorta and its branches. A large number of observers showed that it causes contraction of the coronary vessels. 140. WIGGERS 141. (1911) found that contraction of the arteries of the lungs was produced by the extract although the effect was not pronounced.

FRAENKEL 142. (1914) obtained vasoconstriction of the cerebral vessels, but more recent and more accurate work conducted by FLOREY 143. (1925) has shown that such is not the case. Florey put posterior pituitary extract on the pia mater, and observed the vessels through a microscope and could see no change. He attributes Fraenkel's result to the fact that he included the Circle of Willis in the cerebral vessels perfused.

SCHAFER & HERRING 144. (1908) demonstrated the somewhat interesting fact that the post. pituitary extract causes dilatation of the renal vessels, and this has been corroborated by several other observers. 145. Some of these workers showed additional facts in this connection, such as a primary constriction before the dilatation, while J. PAL 146. (1909) found that pituitary extract causes contraction



of a ring from the proximal part of the renal artery, and relaxation of one from the distal part.

MAGNUS & SCHAFER 147. (1901) demonstrated the fact that injection of posterior pituitary caused contraction of the spleen, but this is probably a nervous phenomenon as shown by De BOER & CARROLL 148. (1924) who placed an isolated spleen in warm Ringer's solution and found that it did not contract on the addition of posterior pituitary extract.

NOEL PATON 149. (1912) observed that the extract produced a fall in blood pressure with birds. This was later confirmed by HOGBEN 150. (1925) while HOGBEN & SCHLAPP 151. (1924) found that with amphibia there was either a fall or no effect.

KROGH & REHBERG 152. (1922) demonstrated that posterior pituitary causes constriction of the capillaries at a strength (1 in 500,000) below that which affects the arteries. KROGH 153. (1922) in his paper on the capillaries, comes to the conclusion that a normal function of the pituitary secretion is to cause constriction of the capillaries and that its presence in the blood serves to regulate the capillary action.

BAINBRIDGE & TREVAN 154. (1917) showed that it caused a fall in pressure in the veins; probably, they surmised, owing to the contraction of the arteries and the capillaries.

It has been found by several observers that the pituitary principles appear quite early in foetal life. M'CORD demonstrated <sup>their</sup> presence in the bovine foetus about the eighth week, 155. while LEWIS 156. (1916) obtained the pressor principle in the foetus of the pig at the tenth week. The earliest period in man has not been experimentally shown, but SHARPEY-SCHAFER is of the opinion that it is probably about the same as in the bovine foetus. 157. (1923). KEENE & HEWER obtained an extract from an eight-week human foetus which produced expansion of the melanophores in the frog, although they were unable to get enough material to determine a pressor effect in the mammal. 158. (1924).



## B. On Plain Muscle.

BLAIR BELL & HICK 159. (1909) appear to have been the first to appreciate the effect of the posterior pituitary on the plain muscle of the viscera. They found that it causes constriction, and their observation has been corroborated by many workers who utilised different sections of the visceral (160.) muscle in order to obtain their confirmatory reports. (i.e. intestine, stomach, oesophagus, gall bladder etc.) while also some observers found the opposite result - inhibition. 161. PANCOAST & HOPKINS 162. (1917) used the X-ray in order to find out the effect of the posterior pituitary on the intestine and their results served to confirm those of Blair Bell and Hick. A.W. YOUNG 163. (1915) found that the extract produced not only a general increase in tone of the intestinal strip, but also increased the force of the pendulum contractions.

A.D. MACDONALD 164. (1925) helped in the advancement of our knowledge regarding the pituitary, when by considering the effects caused by a series of different extractions, he came to the conclusion that the principle stimulating plain muscle was separate from the oxytocic and pressor principles, and that it was probably histamine.

Various workers have observed the effect of the posterior pituitary extract on the different sources of plain muscle found in the body.

DIXON 165. (1923) came to the conclusion that, while stimulating the small intestine, the posterior pituitary inhibited the large. This effect gives rise to defaecation, as first noticed by FODERA & PITTAU 166. in 1909, and by BLAIR BELL & HICK 159. in the same year.

The constricting effect of the extract on the urinary and generative passages has long been realised. FRANKL-HOCHWART & FROHLICH 167. noticed this in connection with the bladder in 1910, while BOTTAZI 168. (1916) corroborated this with the ureter. WADDELL obtained no effect with the extract on the vas deferens, although he got stimulation of the

uterus masculinus in the rabbit. 168. (1913).

Perhaps the most striking effect of the posterior pituitary is its "oxytocic" or "uterine contracting" power, first noticed by DALE 169. in 1903 and since corroborated with various additional details by many workers. 170. This property of posterior pituitary is used in order to standardise extracts, the first workers to make use of this being DALE & LAIDLAW 171. (1912). They were followed by others 172. while SMITH & M'CLOSKEY 173. (1924) have made a study of the different methods of standardisation, and have published a paper on the subject. It has been shown by EVANS & SIMPSON 174. (1923) that the posterior pituitary increases in amount after the seventh month of pregnancy, and it has been surmised that its uterine contracting power helps in the onset of parturition. GALLIE & SCOTT 175. (1920) have shown that repeated administration during pregnancy may produce abortion, or at the end of pregnancy may initiate labour.

Other workers 176. have shown that the posterior pituitary causes contraction of the muscular tissue of the respiratory apparatus (i.e. trachea and bronchioles) and KOLLS & GELLING 177. (1924) have proved that this is due to the histamine present in the preparation.

DALE 178. (1909) and other observers 179. have shown that intravenous injection of the posterior pituitary extract causes contraction of the iris, which quickly passes off, while if instilled into the conjunctiva, both ARGANARAZ 180. (1913) and POLLOCK 181. (1920) found that dilatation occurs. CRAMER 182. (1908) also obtained dilatation on adding posterior pituitary extract to Ringer's solution surrounding an excised eye.

#### C. On Blood.

Various workers have observed changes in the relative amounts of the constituents of blood after the injection of posterior lobe extract, but FEISSLY 183. (1922) showed that this effect is produced

by most extracts. LIVON 184. (1909) found that the posterior lobe extracts increase the coagulability of the blood, while anterior lobe extracts did not have the same effect. These results have been corroborated by various workers, some of whom performed their experiments "in vitro" 185.

#### D. On Secretion.

DIXON & HALLIBURTON. 186. after long experiments concluded that the posterior pituitary extract had no effect on the secretion of cerebro-spinal fluid. This has been verified by BECHT 187. (1920) who in addition found that the extract is a lymphagogue - possibly due to its stimulating effect on the muscles of the lymphatic system.

Several workers have obtained somewhat conflicting results with regard to the effect of the posterior pituitary on the alimentary secretions.

##### With Salivary Secretion.

OLIVER & SCHAFER 18. (1895) found that there was no effect, while SOLEM & DOMMEN 188. (1915) found that there was diminution.

##### With Gastric Secretion.

HOUSSAY 189. (1913) found that there was an increase but most of the other workers 190. obtained inhibition of the flow of secretion.

##### With Pancreatic Juice.

SCHAFER & HERRING 191. (1903) found that there was either diminution or no effect, while PEMBERTON & SWEET 192. (1910) found that there was inhibition of the secretion of the juice excited by the introduction of acid into the duodenum.

The posterior pituitary has long been known to have a milk expulsion effect. OPT & SCOTT 193. showed this in 1910 and it has since been confirmed by several workers. 194. GAVIN 195. in 1913 showed that the extract had probably no direct galactagogue effect, but rather expelled the milk present by constricting the lacteals. GAINES 196. (1915) found that the extract caused an increase in pressure at the nipple. Various observers have

corroborated the fact that increased flow of milk occurs under the influence of the autacoid, 197.

There may be a slight galactagogue effect as shown by SCHAFER 198.(1912) who found that the electrical changes occurring in the mammary gland at excretion were similar to those in secretory glands when secretion was occurring.

#### E. Diuretic--Antidiuretic.

Many workers 199. have shown that the injection of posterior pituitary into an anaesthetised animal is accompanied by a large increase in the flow of urine.

HERRING 200.(1914) says that only extracts of pars nervosa have this power, and that those of partes intermedia and anterior do not produce diuresis.

Two contrary schools of thought have arisen with regard to the reason for the diuretic action.

The first headed by Sharpey-Schafer and Herring hold that the pituitary has some direct action on the kidney cells, so increasing their output of urine. The diuretic effect of the pituitary autacoid is not antagonised by atropine, and, as SHARPEY-SCHAFER 201.(1926) pointed out, this may be taken as a sign that it does not act through nerves or through nerve endings, but directly on the kidney cells; There can be quoted in confirmation of this view the work of CUSHNY & LAMBIE 202.(1921) who found that the diuresis was proportional to the rate of blood flow through the kidney. (N.B. proportional to the rate of flow, and not to the blood pressure). HOSKINS & MEANS 203.(1913) found that there was no direct relationship between the blood pressure and the diuresis. STOLAND & KORB 204.(1921) as the result of a series of experiments were able to state that the injection of posterior lobe extracts caused differences in the constituents of the urine, and this, they concluded, could only be due to the action of the extract on the kidney cells themselves. MONAKOW 205.



MONAKOW 205. (1921) has described two cases where injury to the pituitary was accompanied by degeneration of the cells of the convoluted tubules.

Other workers 206, have confirmed this view, while STARLING & VERNEY 207. (1925) and STEHLE & BOURNE 208. (1925) conclude that the pituitary is the regulator of the output of water and chlorine products.

The other school hold that the flow of urine is in direct relation to the pressure of the blood passing through the kidney, and have several observations to support their view. KING & STOLAND 209. (1913) and HOUGHTON & MERRILL 210. (1908) found that the diuresis was directly related to the volume of the kidney, and this, they say is proportional to the blood pressure.

KNOWLTON & SILVERMAN 211. (1913) found that diuresis, caused by pituitary injections, was unaccompanied by an increase in oxygen consumption, and hence disregarded the view that there was functional activity of the renal cells.

In addition to the diuretic action of the posterior pituitary, there is a distinct anti-diuretic action. This was first noticed in clinical cases of diabetes insipidus, and the first records of this were published separately by FARINI 212, and VELDEN 213, in the same year. (1913). BARKER & MOSENTHAL 214. (1917) suggest that the pars intermedia yields the antidiuretic principle, but they bring forward no proof of their statement.

The antidiuretic effect is not readily seen in normal people, but it has been shown to occur with subcutaneous, rather than intravenous injection by HOUSSAY, GALAN & NEGRETE. 215. (1920). ADDIS in conjunction with several other workers (216.) has shown that subcutaneous injection checks the urea secretion.

The antidiuretic effect has been verified by several observers, some of whom created artificial "water diuresis" by giving excess of water to drink, and in this way, PRIESTLEY 217. (1921) after

administering posterior lobe extract subcutaneously, obtained antidiuresis for four to six hours. Similar results have been obtained by BRUNN 218. (1920) and by M'BRAYER. 219. (1921).

It is a matter of doubt as to where the water is stored during the antidiuretic period. REES 220. (1918) thinks that the antidiuresis is due to delay in the absorption from the intestine, but CRAIG 221. (1925) has published a paper which completely disproves this theory.

MOTZFELDT 222. (1917) found that there was no antidiuresis if the splanchnic nerves were severed.

PICK 223. (1924) finds that after taking excess of water, the volume of the blood is not increased, and concludes that the water is absorbed by the protein colloids of the tissues and of the liver. MOLITOR & PICK 224. (1924) found that the antidiuretic effects could be at once removed by administering urea, and hence concluded that the antidiuresis had nothing to do with the kidney, but is an effect of the tissues. This has been corroborated by BRUNN 225. (1921) and also by HOFMANN. 226. (1921) and both state that in their opinion, the pituitary serves as a water regulator of the tissues in general.

#### F. On Growth.

The posterior pituitary has been definitely shown to be detrimental to growth by several workers. (227.) Animals fed on posterior lobe extract have their growth retarded, as shown by ALLEN 228. (1920) in tadpoles and UHLENHUTH 229. (1920) in axolotls.

GOETSCH 227. (1918) found that in addition to retardation of growth, there was marked retardation of the development of the sexual organs when the animal was fed on posterior lobe. He obtained the opposite result on feeding with anterior lobe, while MARINUS 230. (1919) found that there was little or no effect on feeding with extracts from pars tuberalis.

#### G. On Metabolism.

## G. On Metabolism.

One of the first to test the influence of the pituitary on metabolism was MALCOLM 231. (1903) however his results were somewhat variable. THOMSON & JOHNSON 232. (1903) found that metabolism was stimulated. FRANCHINI 233. (1910) obtained an increase in the excretion of Calcium, Magnesium and Phosphorus. Various other observers furthered this work. (234.) C. A. Mc. KINLAY 235. (1921) showed that the basal metabolism was increased with subcutaneous injection of the posterior pituitary.

BORCHARDT 236. (1908) was the first worker to describe the production of glycosuria as a result of the injection of posterior lobe extract. OTT 237. confirmed these observations, but several other observers have contested them. (238.) GOETSCH, CUSHING & JACOBSON 92. (1911) found that the limit of assimilation for sugar was lowered, but in opposition to this is the fact that the glycosuria caused by ether or by adrenaline is inhibited, as shown by MELLANBY 239. (1919) and by STENSTROM 238. (1913) respectively.

## H. On Body Heat.

CUSHING and fellow workers (92.) in 1911 found that the posterior pituitary extract caused a rise in the body temperature, while ROGERS 240. (1922) verified these results in pigeons. HASHIMOTO 241. (1924) found that removal of the pituitary in mammals was followed by a fall in temperature, and the injection of posterior pituitary after this operation caused the temperature to rise back to normal; in unoperated animals however, the injection either had no effect or gave rise to a fall in temperature, and hence Hashimoto regards it as one of the functions of the pituitary to regulate the body temperature by influencing the excitability of the heat centres in the brain. Cushing suggests that hibernation may be brought about by a deficiency in its secretion, and in support of this theory there is the observation of CUSHING & GOETSCH 242. (1915) that during hibernation,

the cells are smaller than usual and have deeply staining nuclei.

BIEDL 243. (1923) has shown that the extract causes a rise in the respiratory quotient if the animal is well nourished, and a decrease if it is badly nourished.

#### I. On the Pigment Cells of Amphibia.

HOGBEN 244. (1924) conducted a series of experiments in this direction, and found that when the posterior pituitary was removed the frog became pale and was unable to adapt itself to its surroundings while injection of posterior lobe extract makes the animal become uniformly dark. The exact opposite is the case with adremaline, and hence it is assumed that the two autacoids control the "pigmentary effector system." Most of the work in this direction has been done by Hogben in coordination with other workers, while similar experiments have been conducted with toads by HOUSSAY and co-operators 245. (1924), corroborative results being obtained.

B. M. ALLEN. 246. (1924) found that removal of the pituitary in tadpoles affects not only the body, but the brain retains its larval form to a certain extent.

HERRING 247. (1913) believed that there were at least two different principles, and that the pressor substance is present mainly in pars nervosa, while the oxytocic is present in pars intermedia. He thought that the material for both is produced by the epithelium of the pars intermedia, and that this material becomes chemically changed in its passage through pars nervosa. According to him the oxytocic substance is already formed in pars intermedia, but the pressor substance is a product of the chemical changes in the pars nervosa, and is only found there. HOGBEN & De BOER 248. (1925) have confirmed this view. ATWELL & MARINUS 249. (1918) find that the pars tuberalis has little physiological activity, but ABEL 250. (1924) believes that the pituitary hormone is situated there.



# HISTORY OF THE DISCOVERY OF THE EFFECTS OF THE ANTERIOR LOBE.

FREIDREICH 10. in 1865 appears to have been the first to associate abnormal growth with enlargement of the anterior lobe of the pituitary, and since that time various experiments have been made which tend to strengthen this view that the anterior pituitary is associated with the control of growth. Grafting experiments, conducted by CUSHING 251. (1909) and collaborators must be mentioned, while CERLETTI 252. (1906) and GOETSCH 253. (1913) have both found that growth is stimulated by feeding animals on anterior pituitary. SCHAFER 254. (1912) confirmed this if the feeding was sustained for a reasonable length of time, but stated that an appreciable period must elapse before any distinction between the pituitary-fed and the control animals becomes manifest. Other workers have corroborated these results. (255.) C. S. SMITH 256. (1923) however could observe no effect in way of acceleration of growth or of sexual development, on feeding young white rats for a prolonged period on pituitary.

MARINUS 230. (1919) found that pars tuberalis tends to diminish growth and has no effect on the sexual development, while several observers have brought forward conflicting evidence as to the effect of the anterior pituitary on sexual development. WINTERNITZ 257. (1913) and WULZEN 258. (1914) found that there was abnormal sexual development, while others (PEARL 259. (1913) and MAXWELL 260. (1913)) deny this and indeed found that there was retardation of the growth, if anything. These experiments were conducted to a large extent with birds. L. N. CLARK 261. (1915) found that as a result of feeding laying hens (white leghorns) with anterior pituitary, the numbers of eggs were almost double those furnished by controls of the same breed.

Another group of workers experimented with amphibia and almost all found that metamorphosis was hastened by feeding with the anterior pituitary. These experiments can be divided into different groups dependent on the method of supplying the pituitary. Certain workers fed the amphibia on anterior lobe, (262.) others grafted the anterior lobe into them, (263.) while a third set of observers administered the pituitary by means of the injection of its extract, (264.) With slight modifications the results of all these experiments tend to support one another, and the variances found are possibly due to the differences in the technique adopted.

The growth promoting power of the anterior pituitary was attributed by P. E. SMITH & G. CHENEY, 265. (1921) to the presence of iodine (i.e. analogous to the thyroid). They suggested that this iodine was only to be found in the commercial product, as they failed to obtain any result when they used the fresh gland. HALLIBURTON, CANDLER & SIKES 266. (1909) in confirmation of this latter, proved that no iodine is present in the pituitary, even after the removal of the thyroid. This has been corroborated by many other observers. (267.)

BRAILSFORD ROBERTSON 268. (1916) claims to have extracted from the pituitary a growth promoting principle, which he named "tethelin," but his results have not been confirmed by DRUMMOND & CANAAN 269. (1922) who carried out similar experiments using his technique.

P. E. SMITH 270. (1927) reported a series of investigations on the induction of sexual maturity by pituitary transplants. ZONDEK & ASCHEIM 271. (1927) confirmed this, while more recently, the evidence produced by EVANS & SIMPSON 173. (1928) clearly demonstrates the existence of a separate gonad-stimulating substance.

CUSHING & TEEL 272. (1929) have conclusively shown that the anterior pituitary contains two quite separate principles; - 1) Growth Promoting

and 2.) Sex Stimulating. This latter stimulates the sexual cycle, and can be separated by acid extracts, which, however, destroy the growth promoting principle of the gland. Most of this work has been confirmed by BELLERBY 273. (1929) and extended by PARKES 274. (1929) who showed that when fresh pituitary suspensions are injected into adult females <sup>mammals</sup>, an abnormally large number of ova ripen and oestrus sets in.

EVANS 173. (1928) considers that if the person is pregnant, the anterior pituitary provides the stimulus for retaining the luteal activity for the first seven months, and hence is increased at this period. After the seventh month however, the posterior pituitary increases and becomes gradually more important than the anterior pituitary, and then at the ninth month, the interaction of the posterior pituitary with the interstitial cells of the ovary leads to the onset of parturition.

The first part of this supposition forms the basis of the ZONDEK -- ASCHEIM test for pregnancy. 271. (1927). The urine of a suspected person is injected into an immature mouse, and on killing it seven days later, a corpus luteum will be found if the test is positive, owing to the stimulus from the anterior lobe secretion. The presence of the posterior pituitary in the urine towards the end of pregnancy, can be demonstrated by its oxytocic property, and on its addition to a solution containing Uterine Muscle, the muscle contracts violently.

FEE & PARKES 275. (1929) have recently provided more important evidence to show quite definitely that in rabbits, the anterior pituitary stimulates the sexual cycle.

The work in this particular research is proceeding apace, and it is practically impossible to keep up to date in this respect. However I have attempted above to give a brief resume of the principle discoveries in this sphere.

# HISTORY OF DISCOVERY OF CHEMICAL CONSTITUTION OF PITUITARY AND ATTEMPTS AT THE ISOLATION OF ITS PRINCIPLES.

Several workers have investigated the general chemical constitution of the pituitary, and from the results they obtained attempts have been made to forecast the functions of the gland. Among the observers who did this work, the following were the most prominent;-- MALCOLM 231.(1903), FENGER 276.(1915 and 1916), HOUSSAY 194.(1913) and MACARTHUR 277.(1919). In addition a large number of workers have identified themselves with this side of the subject by showing that no iodine is present in the gland.(266 and 267.)

Among the earlier attempts at the isolation of an active principle from the pituitary must be mentioned those of HOUSSAY 130.(1911) and FUHNER 278.(1913). They obtained crystalline products. Houssay thought that in his case, it was a single substance. Fuhner however claimed to have separated four distinct substances -- the first showed the pressor effect, the second the pressor and a little oxytocic, the third a little pressor and the oxytocic, while the fourth was mainly oxytocic. As a result of this work, it was surmised that the oxytocic and the pressor effects were due to quite distinct substances which could not be properly isolated, probably due to the lack of dissimilarity in their chemical constitution.

DUDLEY 279.(1919) and DALE & DUDLEY 280.(1921) came to similar conclusions, and Dudley showed the immense potency of the posterior pituitary by obtaining positive results while utilising minute quantities.

SCHAFER & VINCENT 122.(1899) found that an alcoholic extract of the posterior lobe had a depressor effect. This has since been confirmed by HOGGEN & SCHLAPP 151.(1924) and they drew attention to the resemblance of this action to that of Histamine. This has been confirmed by ROCA 176.(1921) who found



that the depressor substance could be completely removed by extraction with chloroform, and that the oxytocic principle was left.

ABEL 281.(1928) and his coworkers held that the posterior lobe only contains one specific autacoid, while DUDLEY and his collaborators contended that there was more than one principle.(279 and 280.)

The controversy has been finally settled in favour of the multiple theory by the work in the American laboratories of Parke Davies of KAMM 282.(1928) and his cooperators, who have separated the pressor almost completely from the oxytocic principle. Their method, in brief, is to extract with acetic acid and then fractional precipitation with ether, acetone and petroleum ether. Finally, two fractions were obtained, the first mainly pressor, and the second predominantly oxytocic, and these have now been prepared on the manufacturing scale. It is not yet certain whether or not the small pressor action of the oxytocic fraction is due to traces of the pressor principle and vice-versa, but BURN 283.(1928) has shown that the anti-diuretic effect and insulin-antagonising action are associated only with the vasopressin fraction. GADDUM finds, however, that this fraction has the melanophore-expanding action characteristic of extracts of pars intermedia, and hence is probably not a single principle.(284.)(1928).

#### RECENT WORK.

During the last two years a large amount of confirmatory work has been performed, and, as such, is of little importance for our purpose. I have endeavoured below to give a brief summary of the recent investigations which has been more or less of an original nature. Many omissions must invariably occur however, in my account, owing to the large amount of literature on this subject, and furthermore, it is premature to draw conclusions on many of the claims which have been made owing to lack of confirmatory

evidence.

A great deal of work has been published recently to supplement the view that the pituitary and the diencephalon are intimately related. Such work is more of a theoretical than an experimental nature as most of the authors have used the findings of other observers on which to base their statements.

CUSHING 304. (1930) in his Lister Memorial Lecture emphasises the relationship of the two parts and states that it is almost impossible to consider the one without the other.

It has been shown that the basophil cells produce the sex hormones, but in animals whose larvae undergo a metamorphosis there appears to be a separate hormone which directs this change. As the mammalian pituitary will produce metamorphosis in the tadpole the hormone responsible must be present even in animals where such a change does not occur. The thyroid of an animal metamorphosed by anterior pituitary undergoes the changes of normal metamorphosis, as shown by UHLENHUTH 262, while ALLEN 228, and others have found that the thyroid of a hypophysectomised animal atrophies, but is regenerated by implantation of an anterior pituitary. LANGDON BROWN 305. (1930) concludes that the extracts of anterior lobe which induce metamorphosis are those which increase the metabolic rate, as would be expected if such extracts acted on the thyroid and CREW & WEISNER 306. have separated it from the sex hormones.

A certain amount of work has been done to confirm the relationship of the ovarian and the pituitary hormones. COLLIP 307. (1930) finds that the transplantation of the anterior lobe of the pituitary into muscle liberates oestrin from the ovaries of an immature animal. ENGLE 308. (1929) points out that whereas anterior lobe transplants have the effects as described by Collip above, the injection of the urine of a pregnant animal causes folliculation followed by the formation of a corpus luteum with retention of the ovum within it. It is therefore, difficult to attribute

both results to the same anterior lobe principle. C.F. FLUEHMANN 309. (1929) finds large amounts of anterior pituitary autacoid in the blood after extirpation of the ovaries and the serum of such blood will excite ovulation in the immature mouse; he therefore suggests that the pituitary hormone is acting in a compensatory manner to the ovarian principle.

The following is a chronological arrangement of important contributions to literature on the pituitary gland <sup>before 1900</sup> as given in BARKER'S "Endocrinology and Metabolism". Only the workers are given. (For publications see the Bibliography.)

- <sup>nd.</sup>  
2 century - GALEN. Thought that nasal secretions  
285. originated in the pituitary.
1543. VESALIUS, A. Upheld Galen's idea.
- <sup>286.</sup>  
1660-62. SCHNEIDER, C. Overthrew Galen's idea and  
287. stated that nasal secretions  
do not originate in the  
pituitary body.
1672. LOWER, R. Supported Schneider's view.
- <sup>288.</sup>  
1682. WILLIS, T. Observed abnormalities in the  
289. size of the pituitary body.
1700. BONETUS, T. Reported a case of hypophyseal  
290. tumour.
1705. VIEUSSENS, R. Reported a case of tumour of  
291. the hypophysis with amaurosis  
and epileptiform movements.
1718. PETIT. Found the gland "squirrheuse"  
292. in subjects with hydrocephalous.
1724. WEPFER, J. J. Gave a description of anatomical  
293. abnormalities of the pituitary.
1769. DeHAEN, A. Mentioned amenorrhoea in  
294. connection with hypophyseal  
tumour.
1779. MORGAGNI, G. B. Mentions a light-yellow tint  
295. of the gland which occurs under  
certain circumstances.
1781. GREGEDING, C. G. Noted changes of the hypophysis  
296. in epilepsy.
1802. WENZEL, J. Attributed epilepsy to changes  
7. in the pituitary, which gland  
he considered most important.



1811. WENZEL, J. Found the infundibulum reddened  
297. and inflamed in an epileptic.
1823. RAYER, P. Published a collection of cases  
293. of hypophyseal disorder prior  
to 1823.
1823. WARD, J. Reported a case of amaurosis  
299. produced by enlargement of the  
pituitary.
1833. HEDLUND. Reported a case of hypertrophy  
300. of the pituitary with blindness.
1840. MOHR, B. Described a case of hypophyseal  
113. tumour with obesity, visual  
disturbance, headaches, vertigo,  
clumsy movements and mental  
symptoms.
1855. HARVEY, J. R. Described a sudden and complete  
301. amaurosis result of pituitary  
abscess and a scrofulous tumour.
1863. LEBER, T. Quoted a case of optic neuritis  
302. and bilateral abducent paralysis  
with gliosarcoma of the infund-  
ibulum and tuber cinereum.
1886. MARIE, P. Described the syndrome of  
9. acromegaly.
1887. OPHTHAL. SOC. Discussed pituitary lesions in  
of the U.K. relation to eye symptoms, obes-  
117. ity, menstrual disturbances and  
mental manifestations.
1889. ROGOWITSCH, N. Noted hypertrophy of the pituit-  
303. ary after removal of the thyroid.
1890. NEW TREND. Study of the anatomical aspect.
1895. OLIVER & Discovered that the pituitary  
SCHAFFER. was a gland of internal secretion.  
13.
1898. COMTE, L. Observed that the anterior lobe  
29. enlarges during pregnancy.
1899. OPPENHEIM Confirmed this by means of X-ray.  
108.

There were so many workers that entered this field of research after 1900 that it is practically impossible to give a complete list of their names and of their work, and so the following is a chronological arrangement of only the more important contributions to literature on the pituitary gland after 1900. (Only the names of the workers are given; for publications, see the bibliography.)

- |       |                                 |   |
|-------|---------------------------------|---|
| 1900. | BENDA.<br>107.                  | Pointed out that pituitary tumours are adenomatous in nature.                               |
| 1901. | FROHLICH, A.<br>86.             | Described the syndrome; - obesity, infantile genitalia etc. with pituitary tumour.          |
| 1902. | MAGNUS & SCHAFER.<br>147.       | Demonstrated that the post. pituitary caused contraction of the spleen.                     |
| 1903. | MALCOLM.<br>231.                | Investigated the chemistry of the pituitary body.   |
| 1903. | GENTES.<br>55.                  | Published an account of the blood vessels of the gland.                                     |
| 1904. | LAUNOIS.<br>21.                 | Studied the histology of the gland and brought to notice several new facts.                 |
| 1904. | HERRING.<br>131.                | Realised the effect of the posterior pituitary on the circulatory system.                   |
| 1905. | THOMPSON &<br>JOHNSTON.<br>232. | Found that the posterior pituitary stimulated the metabolism.                               |
| 1905. | FICHERA, G.<br>62.              | As a result of experiments on hens, concluded that the hypophysis is not essential to life. |
| 1906. | PAULESCO.<br>70.                | Introduced the lateral approach for hypophysectomy.   |

1906. DALLÉ, H. H. Demonstrated the oxytocic effect  
169. of the posterior pituitary for  
the first time.
1907. CERLETTI. Appreciated the growth-promoting  
252. power of the anterior pituitary.
1907. PAULESCO. Was the first to state that  
70. complete removal of the pituitary is always fatal.
1908. HERRING. Pointed out the existence of  
38. vesicles, and of "Herring's  
Bodies" in pars intermedia.
1908. BARTELS. Gave the name of "Dystrophia  
114. Adiposa Genitalis" to Frohlich's  
Syndrome.
1908. PARISOT. Showed that subcutaneous inject-  
136. ion of posterior lobe extract  
gives slowing of the heart with  
a gradual rise in blood pressure.
1908. SCHAFER & Found that the posterior  
HERRING. pituitary dilated the renal  
144. vessels.
1908. BORCHARDT. Was the first to describe glycos-  
236. uria following posterior lobe  
injection.
1909. SANDRI. Pointed out that the posterior  
227. pituitary is detrimental to  
growth.
1909. LIVON. Showed the blood-coagulating  
184. power of posterior pituitary.
1909. BELL & HICK. Observed the effect of the post.  
159. pituitary as a constrictor of  
plain muscle.
1909. HALLIBURTON, Showed that there is no iodine  
CANDLER & SIKES. in the pituitary.  
266.

1910. OTT & SCOTT. Demonstrated the milk expelling  
193. effect of the posterior pituitary.
1910. CUSHING & Showed that the same active  
GOETSCH, principles are present in both  
45. the C.S.F. and the posterior  
pituitary.
1911. TILNEY. Was the first worker to describe  
37. pars intermedia in detail.
1911. OTT. Published a book on pituitary  
237. and confirmed Borchardt's results.
1911. CUSHING. Found that posterior pituitary  
92. caused a rise in body temperature.
1912. MARK. Published his book on Acromegaly.  
109. as a personal experience.
1912. CUSHING. Pointed out that polyuria often  
90. follows a pituitary lesion.
1912. ASCHNER. Did not find the gland essential  
77. to life, and clearly demonstrated  
its growth controlling property.
1913. BEGO & PLUMIER. Showed that the posterior pit-  
128. uitary causes slowing of the  
heart.
1913. GAVIN. Found that the posterior pit-  
195. uitary extract had no direct  
galactagogue effect.
1913. FUHNER. 278. Attempted to isolate the principles.
1913. HERRING. Believed that there were two  
247. distinct principles in the post.  
lobe, confined to the different  
200. parts, and that diuresis is  
caused by pars nervosa.
1914. FRAENKEL. Found that posterior pituitary  
142. constricted the cerebral vessels.



1914. WULZEN, 253. Found that excess of anterior pituitary caused precocious sexual development.
1915. CLARK, 261. Confirmed this with hens.
1915. M'CORD, 155. Showed that the principles appear in the pituitary early in foetal life.
1916. GOETSCH, 227. Found that posterior pituitary feeding caused retardation of sexual growth.
1917. BARKER & MOSENTHAL, 214. Suggest that pars intermedia yields the anti-diuretic principle.
1918. ATWELL & MARINUS, 249. Found that pars tuberalis has little physiological activity.
1918. OEHME, 50. Showed that the C.S.F. contains a vaso-constrictor principle.
1919. BLAIR BELL, 72. Published a book on the pituitary body.
1919. DUDLEY, 279. Demonstrated the potency of the posterior pituitary.
1920. GALLIE & SCOTT, 175. Found that excess of posterior pituitary during pregnancy produces abortion.
1921. MONAKOW, 205. Found that injury to the pituitary was accompanied by degeneration of the cells of the kidney.
1921. DALE & DUDLEY, 230. Held the view that there is more than one principle in the pituitary.
1922. KROGH, 153. Concludes that the pituitary serves to regulate the capillary action.

1922. REISS. Suggested that there were two  
22. types of secretion, a) into the  
C.S.F. and b) into the blood.
1922. CAMUS & ROUSSY. Held that the conditions which  
93. are attributed to the pituitary  
should be attributed to the  
tuber cinereum.
1923. WINTON & Demonstrated the melanophore-  
HOGGEN. expanding property of the post-  
79. erior pituitary.
1923. NUVOLI. Produced rickets in rabbits by  
89. exposing the pituitary to X-rays.
1923. ABEL. Held that there is only one  
281. autacoid in the pituitary.
1924. SMITH & Published a paper on the stand-  
173. M'CLOSKEY. ardisation of pituitary extracts.
1924. ABEL & GEILING. Obtained similar results with  
133. the infundibulum as with the  
pituitary.
1924. ABEL. Concludes that the pituitary  
250. hormone is situated in pars  
tuberalis.
1924. FRANK. Stresses the importance of pars  
101. tuberalis.
1924. TRENDLENBURG. Showed that the C.S.F. contains  
49. an oxytocic principle.
1925. FLOREY. Found that the posterior pituit-  
148. ary does not cause constriction  
of the cerebral vessels.
1925. MACDONALD, A. D. Concluded that the principle  
164. stimulating plain muscle is  
probably histamine.
1926. SHARPEY-SCHAFER. Supported the view that the post.  
201. pituitary acted directly on the  
Kidney to give the diuretic  
action.

1926. SHARPEY-SCHAFFER. Holds that Frohlich's Syndrome  
120. is due to deficiency of post.  
lobe secretion.
1927. SMITH, P. E. Produced sexual maturity by  
270. pituitary transplants.
1927. ZONDEK & Evolved their test for pregnancy  
ASCHEIM. dependent on the gonad stimu-  
271. ating substance of the anterior  
pituitary.
1928. KAMM. Upheld Dudley's multiple  
282. principle theory for the post-  
erior pituitary.
1928. BURN. 283.  
and Both supported Dudley's view.
1928. GADDUM. 284.
1928. EVANS & Showed that the posterior  
SIMPSON. pituitary increases proportion-  
174. ally after the seventh month  
of pregnancy.
1929. CUSHING & Have shown that the anterior  
TEEL. pituitary contains two separate  
272. principles, a) Growth Promoting  
b) Sex Stimulating.
1929. BELLERBY. 273. Confirms these results.
1929. PARKES. 274. Has extended the work. Later  
he worked in conjunction with  
1929. FEE & PARKES. Fee, and their work is still  
275. proceeding.
1929. ENGLE. Finds that injection of the  
283. urine of a pregnant animal  
causes formation of corpus  
luteum with retention of ovum.
1929. FLUHMAN. Suggests that the pituitary  
289. hormone acts as a compensator  
to the ovarian principle.

1930. COLLIP, 807. Obtained liberation of oestrin on transplanting anterior pituitary into an immature animal.
1930. CUSHING, 804. Emphasises the connection between the diencephalon and the pituitary.
1930. CREW & WEISNER, 806. Have separated from the anterior lobe a hormone acting on the thyroid, and causing metamorphosis.



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